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Analgesia use during pregnancy and risk of cryptorchidism: a systematic review and meta-analysis

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Abstract

STUDY QUESTION

Are boys who are born to mothers who use analgesics during pregnancy at increased risk of cryptorchidism compared to those born to mothers who do not take analgesia?

SUMMARY ANSWER

In this systematic review and meta-analysis of 10 published studies, we observed only weak evidence of an association between analgesia use during pregnancy and risk of cryptorchidism in the son.

WHAT IS KNOWN ALREADY

Concentrations of analgesia relevant to human exposure have been implicated as causing endocrine disturbances in the developing foetal testis. However, when viewed collectively there appears to be conflicting evidence regarding an association between maternal use of analgesics and development of cryptorchidism.

STUDY DESIGN, SIZE, DURATION

A systematic review and meta-analysis of studies on analgesia use during pregnancy and risk of cryptorchidism was performed. The search terms used were (analges* OR paracetamol OR acetaminophen) AND (cryptorchidism OR cryptorchism OR undescended test* OR non-descended test* OR non descended test*) for the databases Ovid Medline, Embase, Scopus and Web of Science. The search included all published articles up until 23 May 2016 and no limits were set in terms of language.

PARTICIPANTS/MATERIALS, SETTING, METHODS

Abstracts were screened by one reviewer to remove irrelevant studies, with a 10% random sample of these verified by a second reviewer. The full text of all remaining papers was assessed by two reviewers. Abstracts included in the final analysis were studies which reported associations between the exposure (analgesia) and the outcome (cryptorchidism). Studies were only included if data were provided from which summary associations (odds ratios (ORs) or relative risks) and their 95% CIs could be calculated, or if summary associations were provided by the authors themselves. For each included study, two reviewers independently extracted study meta-data in line with PRISMA recommendations. We assessed study quality and potential for bias using the criteria outlined in the Newcastle-Ottawa Quality Assessment Scale, but did not determine a quality score. Two reviewers independently assessed study quality against these criteria.

MAIN RESULTS AND THE ROLE OF CHANCE

After screening 350 manuscripts, 10 were included in our review (5 case-control studies, 5 cohort studies). We observed weak evidence of an association between ever use of analgesia and risk of cryptorchidism (pooled crude OR: 1.11, 95% CI: 1.00–1.23), with case-control studies revealing a marginally stronger association (1.23, 95% CI: 0.85–1.78) than cohort studies (1.09, 95% CI: 0.97–1.22). We observed weak evidence of a dose-response relationship between increasing weeks of analgesia exposure and risk of cryptorchidism, as well as weak evidence of an effect of timing on analgesia exposure and risk of cryptorchidism. Assessment of study quality via the Newcastle-Ottawa criteria revealed little (if any) evidence of substantial bias that may have meaningfully affected a given study's results.

LIMITATIONS, REASONS FOR CAUTION

While confounding does not appear to be important, misclassification of the exposure is possibly an important source of measurement error in this context. The systematic review is open to reporting bias. Owing to scant data, no meta-analyses for two key questions (relating to dose-response and timing of exposure) could be performed. Medications were grouped based on their common effect and this offers little insight into the relation between specific types of analgesia and cryptorchidism. Finally, there are limitations in assuming that analgesia use reported by mothers is synonymous with actual intrauterine exposure.

WIDER IMPLICATIONS OF THE FINDINGS

The ubiquity of analgesia use during pregnancy makes this exposure particularly important from a population health perspective. About 9 of the 10 studies were conducted in Europe or USA, limiting generalizability of our observations. While the observations from our systematic review and meta-analysis suggest that analgesia use during pregnancy is not strongly associated with cryptorchidism development in the son, they also highlight the need for further detailed assessments of this relationship.

Keywords: cryptorchidism, cryptorchism, analgesia, painkiller, paracetamol, congenital abnormality, pregnancy

Introduction

Although rare in absolute terms, cryptorchidism—failure of the testes to descend permanently into their terminal scrotal position—is one of the most common congenital anomalies to affect boys (Ansell *et al*., 1992). Cryptorchidism is one of the few known risk factors for testicular cancer, wherein males who have suffered cryptorchidism are nearly five times more likely to develop testicular cancer than those who have not (relative risk: 4.8, 95% CI: 4.0–15.7) (Dieckmann and Pichlmeier, 2004). Cryptorchidism is also a risk factor for sub-fertility: men with a history of cryptorchidism are twice as likely to be sub-fertile (10.5%) compared to those without cryptorchidism (5.4%) (Lee *et al*., 1996). Risk factors for cryptorchidism remain unclear, but may be related to disruptions to normal endocrine function sometime during the two phases of testicular descent (8–15 weeks and 25–35 weeks gestation, respectively) (Hutson *et al*., 2016).

The use of medicines to relieve pain—collectively referred to as analgesics—is ubiquitous: a recent study of nearly 40 000 Norwegian adults observed that 47% took an over-the-counter analgesic at least once per week, the most common being paracetamol (also known as acetaminophen) (Dale *et*

al., 2015). Use is also common in pregnancy: in a study of 47 000 mothers of boys, Jensen *et al*. (2010) observed that 55% had taken either acetaminophen, ibuprofen or acetylsalicylic acid at some point during pregnancy.

Analgesics have been implicated as endocrine disruptors, and it has been shown that concentrations relevant to human exposure can cause endocrine disturbances in the foetal testis (Mazaud-Guittot *et al*., 2013). Several studies have observed a positive association between maternal use of analgesics and subsequent development of cryptorchidism in their sons (Berkowitz and Lapinski, 1996; Jensen *et al*., 2010; Kristensen *et al*., 2011; Snijder *et al*., 2012). For example, Snijder *et al*. (2012) observed that women who used mild analgesics during their second trimester had more than twice the odds of giving birth to sons who had cryptorchidism (adjusted odds ratio (OR): 2.12, 95% CI: 1.17–3.83), and that up to 24% of all cryptorchidism cases in their cohort could be attributed to maternal use of mild analgesics during pregnancy.

However, there is conflicting evidence regarding this relationship, with several authors finding no (Mori *et al*., 1992; Wagner-Mahler *et al*., 2011) or weak/limited (Davies *et al*., 1986; Rebordosa *et al*., 2008; Philippat *et al*., 2011) evidence of an association. Thus, the following questions remain unanswered: are boys who are born to mothers who use analgesia during pregnancy at increased risk of cryptorchidism compared to those born to mothers who do not? If an association exists, does the risk of cryptorchidism increase with increasing levels of maternal analgesia use? Finally, does the timing of maternal analgesia use (e.g. by trimester) affect the risk of cryptorchidism?

In order to address these questions, we conducted a systematic review and meta-analysis of studies of maternal analgesia use and development of cryptorchidism in the son.

Materials and Methods

Search strategy

This study was performed in accordance with PRISMA guidelines (Moher *et al*., 2009) and registered with PROSPERO: CRD42016041414, describing in advance the aims and methods of our investigation (Gurney *et al*., 2016).

Eligibility criteria

The PICOS (**P**atient/**P**articipant, **I**ntervention, **C**omparator, **O**utcome, **S**tudy design) criteria used are outlined (Supplementary Table S1). Abstracts in the final analysis included studies which reported associations between the exposure (analgesia) and the outcome (cryptorchidism), with no limit on study design. Studies were only included if data were provided from which summary associations (ORs or relative risks) and their 95% CIs could be calculated, or if these summary associations were provided by the authors themselves.

Information sources

A systematic review was conducted on 23 May 2016 for all articles published up until that time. No limits were set in terms of language used during the initial abstract search. Our search was conducted using Ovid Medline, Embase, Scopus and Web of Science databases. The reference list of studies considered eligible for inclusion were scanned for additional relevant studies. International experts in the field (K.M., L.R.) scanned the list of those studies which met our inclusion criteria to identify any studies missed by our search.

Search terms

Using a Boolean approach, we searched the electronic databases for each possible combination of the following keywords (* indicates 'explosion' term): (analges* OR paracetamol OR acetaminophen) AND (cryptorchidism OR cryptorchism OR undescended test* OR non-descended test* OR non descended test*) (Supplementary Table SII). References were collected and logged in EndNote vX7.1 (Thomson Reuters, NY, USA).

Study selection and data extraction

Screening of abstracts

Figure Figure11 shows the flow chart for study identification and inclusion. Duplicate papers were removed prior to abstract screening. Abstracts were screened by J.G. to remove irrelevant studies, with a 10% random sample of these verified by V.S. The full text of all remaining papers was assessed by J.G. and V.S. to identify those meeting our inclusion criteria. Any disagreements about inclusion were resolved by referral to D.S. All papers considered relevant during abstract screening but ineligible for final inclusion are listed in Supplementary Table SIII.

Data extraction

For each included study, J.G. and V.S. independently extracted study meta-data in line with PRISMA recommendations. Data items for which there was any disagreement between the two reviewers were referred to D.S.

Assessment of risk of bias (individual and across studies)

In the absence of a gold standard, it has been recommended that any tools used to measure study quality should be as specific as possible to the given topic, and involve a simple checklist as opposed to a scale or score (Sanderson *et al*., 2007). Given these factors, we assessed study quality and potential for bias using the criteria outlined in the Newcastle-Ottawa Quality Assessment Scale (Wells *et al*., 2004; Alam *et al*., 2010), but did not determine a quality score (Burkey *et al*., 2014). J.G. and V.S. independently assessed study quality against these criteria, with disagreements resolved by referral to D.S.

Statistical analysis

In those instances where it was feasible to conduct meta-analyses, we calculated crude ORs and their 95% CIs. This was for two reasons: first, the included studies varied in their reporting of risk estimates, with some reporting ORs and one study reporting hazard ratios (HRs). Second, there was heterogeneity among studies in terms of adjustment for confounding, with some studies not adjusting for confounding whatsoever.

Since not all studies provided crude ORs, these were calculated from tabulated data provided in the manuscripts. Using a random-effects model, we applied inverse-variance weighted methods for combining results across included studies to arrive at a final summary OR (and 95% CIs). We tested for evidence of heterogeneity among studies using both the χ^2 test (with a lower *P*-value indicating high inter-study heterogeneity) (Kirkwood and Sterne, 2003) and I^2 index (0% indicating no inter-study heterogeneity) (Alam *et al*., 2010). We also generated and visually inspected funnel plots for evidence of publication bias.

Meta-analysis was completed in Stata v11.2 (StataCorp, TX, USA) using the *metan* and *metafunnel* functions (Sterne *et al*., 2006).

Results

We identified 10 manuscripts that reported associations between analgesia use during pregnancy and risk of cryptorchidism in the son (Fig. (Fig.1),1), of which 5 were case-control studies (Davies *et al*., 1986; Mori *et al*., 1992; Berkowitz and Lapinski, 1996; Banhidy *et al*., 2007; Wagner-Mahler *et al*., 2011) and 5 were cohort studies (Rebordosa *et al*., 2008; Jensen *et al*., 2010; Kristensen *et al*., 2011; Philippat *et al*., 2011; Snijder *et al*., 2012).

Studies were largely conducted among European populations, with eight studies conducted in Europe, one in the USA and one in Japan (Table (TableI).I). In terms of outcome measurement, the vast majority (8 of 10) used clinical diagnosis either at birth or shortly afterward, with only two of the studies (Mori *et al*., 1992; Jensen *et al*., 2010) using orchidopexy to define the occurrence of cryptorchidism. Due to disease rarity many studies had a small sample, with the number of cases ranging from $n = 35$ (Kristensen *et al*., 2011) to $n = 2051$ (Banhidy *et al*., 2007).

Assessment of study quality revealed little (if any) evidence of substantial bias that may have meaningfully affected a given study's results (Supplementary Tables SIV and SV). There was some relatively minor divergence between cases and controls in terms of response rate, with the differences in non-response proportions between cases and controls ranging from 13% to 19%. The use of self-report to measure exposure status is discussed later.

We observed a high degree of heterogeneity among studies in terms of adjustment for confounding.

Ever use of analgesia

A total of 10 (5 case-control and 5 cohort) studies were included in our assessment of the association between ever use of any analgesia during pregnancy and development of cryptorchidism (Table III). The adjusted measures of association presented by these studies ranged from 1.00 (Mori *et al*., 1992) to 1.93 (Berkowitz and Lapinski, 1996) for case-control studies, and 0.74 to 1.43 (Kristensen *et al*., 2011) for cohort studies. Where both crude and adjusted estimates were presented, adjustment for confounding had little if any impact.

Meta-analysis of crude ORs (Fig. (Fig.2)2) revealed little evidence of a strong association between ever use of analgesia during pregnancy and risk of cryptorchidism in the son (pooled crude OR: 1.11, 95% CI: 1.00–1.23; case-control studies: 1.23, 95% CI: 0.85–1.78; cohort studies 1.09, 95% CI: 0.97–1.22). While there was low heterogeneity among cohort studies (I^2 0%, $P = 0.820$), there was some evidence of moderate heterogeneity among case-control studies (I^2 44%, $P = 0.128$). When studies were combined, there was low overall heterogeneity across studies (I^2 0%, $P = 0.46$). A funnel plot revealed no strong evidence of publication bias (Supplementary Fig. S1).

Dose-response

Two studies, both of which were cohort studies, presented data on a possible dose-response association between use of analgesia during pregnancy and development of cryptorchidism (Jensen *et al*., 2010; Kristensen *et al*., 2011).

When investigating cryptorchidism in Danish and Finnish cohorts, Kristensen *et al*. (2011) observed a dose-response association between analgesia use during pregnancy in their Danish cohort (adjusted ORs: 1–2 weeks use [compared to 0 weeks] 1.5, 95% CI: 0.63–3.55; >2 weeks use 2.47, 95% CI: 1.02–5.96) but not in their Finnish cohort (1–2 weeks use 1.21, 95% CI: 0.50–2.90; >2 weeks use 0.56, 95% CI: 0.13–2.45). Jensen *et al*. (2010) also observed a weak dose-response association, although this association marginally attenuated at the most extreme exposure level (adjusted HRs: 1 week [compared to 0 weeks] 1.09, 95% CI: 0.89–1.34; 2–4 weeks 1.01, 95% CI: 0.81–1.28; 5–8 weeks 1.32, 95% CI: 0.97–1.78; 9–12 weeks 1.35, 95% CI: 0.88–2.05; >12 weeks 1.23, 95% CI: 0.90–1.66).

Timing of analgesia exposure

Four (cohort) studies assessed timing of analgesia use and risk of cryptorchidism (Jensen *et al*., 2010; Kristensen *et al*., 2011; Philippat *et al*., 2011; Snijder *et al*., 2012). Where both crude and adjusted estimates were presented adjustment for confounding had only marginal impact.

When investigating risk of cryptorchidism in both a Danish and a Finnish cohort, Kristensen *et al*. (2011) observed a stronger association between use of analgesia during the second trimester (adjusted OR: Danish cohort 2.30, 95% CI: 1.12–4.73; Finnish cohort 1.21, 95% CI: 0.53–2.76) compared to the first (Danish cohort 1.48, 95% CI: 0.66–3.34; Finnish cohort 0.77, 95% CI: 0.26–2.27). Similarly, Jensen *et al*. (2010) observed a stronger association for analgesia use during the second trimester (adjusted HR: 1.17, 95% CI: 0.89–1.54) compared to the first (0.94, 95% CI: 0.75–1.17), but also observed a small attenuation of this association for use during the third trimester (1.08, 95% CI: 0.87–1.33). Snijder *et al*. (2012) observed a stronger association for analgesia use during mid-pregnancy (crude OR: 2.04, 95% CI: 1.15–3.62) compared to early (0.97, 95% CI: 0.38–2.48) and late pregnancy (1.56, 95% CI: 0.80–3.03).

Discussion

Our meta-analysis suggests that ever use (compared to never-use) of analgesia during pregnancy is weakly associated with the development of cryptorchidism (pooled crude OR: 1.11, 95% CI: 1.00–1.23). However, this lack of a clear association may reflect poor exposure specificity, since ever use pools those who may have been exposed only once with those who may have been routinely exposed. This would result in misclassification of the exposure, which is likely to bias the observed associations towards the null.

On the other hand, it is also possible that in retrospective studies mothers with affected sons might overestimate their exposure relative to those with unaffected sons—which could explain the marginally stronger association observed for the case-control studies. However, the difference between these two point estimates is not large (1.23 vs 1.09), suggesting that recall bias is not of substantial importance in this context.

We observed remarkable heterogeneity in the prevalence of ever use between study populations—ranging from near 0% prevalence up to 94% prevalence (Table III). While there was a tendency for this prevalence to be higher in cohort studies (compared to case-control studies), this was not strongly associated with study design. This heterogeneity could reflect wide variation in analgesia ever use between study populations; however, it could also reflect a validity problem with this unit of measurement—in which self-report (particularly retrospective) does not adequately capture the true prevalence of analgesia ever use. Also, we must accept that there are limitations in assuming that analgesia use reported by mothers is synonymous with actual intrauterine exposure by the foetus.

While there were few studies that had investigated a possible dose-response relationship, we did observe a pattern of increasing risk of cryptorchidism with increasing number of weeks of analgesia exposure. However, as with ever use there is likely to be misclassification of the exposure. Ideally, we would measure dosage and frequency of use over the course of a woman's pregnancy; but in this case, the exposure was simply the number of weeks during which any given amount of analgesia was taken.

Finally, we did observe a pattern of increased cryptorchidism risk when analgesia was consumed during the middle of pregnancy (largely coinciding with the second trimester) relative to early and late pregnancy (Jensen *et al*., 2010; Kristensen *et al*., 2011; Snijder *et al*., 2012). Both Jensen *et al*. (2010) and Phillippat *et al*. (2011) observed a somewhat higher risk of cryptorchidism among those exposed to analgesia during early- to mid-pregnancy than those exposed at any time during pregnancy, suggestive of a pathway by which analgesia may disrupt the first phase of testicular descent; however, the risk estimates (adjusted ORs: 1.14 and 1.20, respectively) and their associated CIs suggest that evidence of this scenario is weak. The issues relating to poor exposure measurement are also relevant here.

It was our original intention to conduct separate stratified analyses for those boys diagnosed by clinical examination and those diagnosed via corrective orchidopexy, in an effort to understand whether the relationship between analgesia use and cryptorchidism differed according to disease severity and/or persistence. However, the vast majority (8 of 10) of the included studies used clinical diagnosis at birth (or shortly afterward). Thus, we were unable to examine this relationship in any meaningful way.

Plausibility of analgesia as a cause of cryptorchidism

The biological plausibility of analgesia exposure during pregnancy as a risk factor for cryptorchidism in the son rests on the premise that this exposure disturbs the normal endocrine processes responsible for testicular descent *in utero*. Similar versions of the mechanism by which this disruption is proposed to occur have been put forward in the literature: namely, that cyclooxygenase (COX)-inhibiting analgesia taken during the critical ‘male programming window’ (sometime between 8 and 15 weeks gestation) diminishes normal androgen activity (Kristensen *et al*., 2012), causing a potentially critical disruption to this first phase of testicular descent by interfering with prostaglandin synthesis (Jensen *et al*., 2010; Kristensen *et al*., 2011; Snijder *et al*., 2012).

However, biological plausibility and aetiological reality are not synonymous concepts. Firstly, as noted earlier evidence is unclear regarding the relationship between the timing of analgesia use and cryptorchidism development—somewhat contradicting the hypothesis that analgesia use during the ‘male programming window’ and cryptorchidism development are strongly related. Secondly, there are similarly plausible arguments that suggest maternal analgesia use might cause other congenital anomalies—but there is little evidence that this is actually the case. For example, Rebordosa *et al*. (2008) compared 26 000 children who were exposed to acetaminophen during early pregnancy with 62 000 children who were not, and found no increased risk of congenital abnormality, regardless of whether they were ever-exposed (adjusted HR: 1.01, 95% CI: 0.93–1.08) or exposed for more than 4 weeks during pregnancy (adjusted HR, compared to never-exposed: 1.04. 95% CI: 0.89–1.21).

The weak associations reported here must also be viewed in the context of other research which has found that low-dose aspirin may be protective against other health outcomes, including pre-eclampsia (Henderson *et al*., 2014), as well as the ongoing debate regarding whether pre-conceptual

aspirin use may (or may not) prevent pregnancy loss in high-risk populations (Schisterman *et al*., 2014).

The role of confounding

Adjustment for confounding among those studies that presented both crude and adjusted risk estimates generally had little impact on the strength of the given association. For example, Jensen *et al*. (2010) reported near-identical crude and adjusted HRs despite adjusting for a number of potential confounders. The authors also conducted multiple sensitivity analyses with further potential confounders to their models, but again observed very little variation in terms of association strength (Jensen *et al*., 2011). This suggests that the relationship between analgesia use and risk of cryptorchidism is not noticeably affected by confounding.

Limitations

Our review has limitations. Firstly, like all systematic reviews the current manuscript is open to reporting bias, wherein those studies that observe the strongest effect are more likely to be published. Secondly, because of scant data, we were unable to conduct meta-analyses for two of our key study questions (relating to dose-response and timing of exposure). Thirdly, 9 of the 10 included studies were conducted in either Europe or the US, limiting the generalizability of our observations to non-Western populations.

Lastly, the current review grouped together medications based on their common effect—i.e. analgesia taken to alleviate pain. This grouping is largely in keeping with the idea that COX-inhibiting analgesia diminishes normal androgen activity by interfering with prostaglandin synthesis; however, it is still possible that these medications may be heterogeneous with respect to both the means by, and extent to, which they may affect testicular descent. For example, Jensen *et al.*(2010) observed a moderate association between acetaminophen exposure and cryptorchidism, but little evidence of such an effect from ibuprofen and acetylsalicylic acid. It was our initial intention to stratify our analyses by medication group, but this was abandoned when it was discovered that many of the included manuscripts conflated these medications into an ‘any-use’ category (Table III). Thus, the current review offers little insight into the relationship between specific types of analgesia and cryptorchidism development.

Conclusions

We observed weak evidence of an association between ever use of analgesia and risk of cryptorchidism. Due to the likely mismeasurement of the exposure we cannot rule out the possibility that this measure underestimates the association between a non-trivial dose of analgesic during pregnancy and cryptorchidism. We observed weak evidence of a dose-response relationship between increasing weeks of analgesia exposure and risk of cryptorchidism, but finer-grained assessments (including measurement of actual dosage and frequency of use) are required to substantiate this relationship. We observed weak evidence of an association between the timing of analgesia exposure and risk of cryptorchidism, whereby those boys exposed during early- to mid-pregnancy appeared to be marginally more at risk than those who were ever-exposed; however, risk estimates were close to the null and CIs were wide. This review highlights the need for further detailed assessments of the relationship between maternal analgesia use and risk of cryptorchidism.

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